High-pressure cleaning in pharmaceutical production – a hitherto unjustly neglected technology!

Advantages and huge potential of sustainability and savings

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PEER REVIEW

Abstract

High-pressure cleaning in pharmaceutical manufacturing can play a decisive role in current Good Manufacturing Practice (cGMP) cleaning automation with regards to sustainability and shorten downtimes for equipment facility installations. Significant reduction in media consumption and energy is possible compared to standard and manual cleaning methods. This article gives an overview about the methodology of high-pressure cleaning within pharmaceutical manufacturing processes, its advantages in general and on basis of a case study.

Key Words

- high-pressure cleaning
- cGMP cleaning
- cleaning automation
- IBC cleaning system
- CIP/COP

Introduction

Automation of the cleaning of parts and tools coming from the production of pharmaceutical manufacturing became quite a standard within Good Manufacturing Practice (GMP) productions. Through fully validated cleaning processes and applications, safety could be achieved regarding cleaning success. Current Good Manufacturing Practice (cGMP) parts- and container-washers are available with different sizes of enclosed washing chambers that ensure cleaning success in pharmaceutical production under fully qualified status (fig. 1). Nevertheless, there are applications and parts that cannot be applied to such a washing system because of their size or because of operating with extreme hazardous and toxic active ingredients. Furthermore, there are parts and containers that are contaminated with extremely resistant matter such as coatings for tablets.

cGMP washing systems used in pharmaceutical industry work through chemical cleaning in a wet water-based process. They either use water in different qualities like controlled tap water, purified water (PW), water for injections (WFI), etc., with different temperatures to achieve a cleaning by washing water soluble contaminants away or by applying detergents to the washing water to achieve a solubility of the contaminants in a water or water-detergent-phase. In either way the most used principle is to recirculate water or a water/detergents mixture in washing cycles to wash small parts and containers. While cleaning parts and containers from easy-to-solve substances with water in washing cycles, getting rid of hazardous and/or resistant contamination – if applicable with the washer's

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Figure 1: cGMP parts washer and cGMP washer with parts to clean on stainless steel basket (all figures provided by Tecniplast).

chambers size – often results in significant use of water, energy (mostly heated water) and chemistry (detergents).

As mentioned, to get parts from pharmaceutical processes and applications such as bins and containers cleaned in an automated validated cGMP process by using cGMP washing machines, these items and devices must be brought from the production into the area where the washing machine is installed. Furthermore, the load (parts, bins, containers) must fit into the washing machines washing chamber. There are washing machines which have the capacity to also load medium-size containers, despite a bigger number of parts and bins on a single washing basket. But the size of the chamber of course is the limitation for containers with bigger sizes. These bigger vessels and containers, like standard Intermediate Bulk Containers (IBCs, typically 1 000 l or bigger), stationary mixer and blender, preparation vessels (like fermenter) and fluid bed dryer, must be cleaned in situ (fig. 2). This is called cleaning in place (CIP) methods. Larger production vessels as mentioned above are often cleaned in time-consuming manual cleaning processes because of their size. Using a cGMP washing machine, where parts to get cleaned must be carried to the area where the washing machine is placed, is called cleaning out of place (COP).

To achieve a controlled cleaning of stationary installed vessels and for example IBCs with different size by using CIP there are 2 possible options:

A stationary installed system that is providing the water supply together with optional detergent supplementation. Through high-pressure piping to the point of use this could be easily applied.

Because typically there is more than just one area in a pharmaceutical production where big vessels and containers to get cleaned are located, a more convenient way is to use mobile high-pressure washers. These units are available as cGMP versions working under fully compliant status. In addition, these units can also be used as stationary systems to get high-pressure piped where it is necessary or where the mobile unit cannot be brought to the location of need. Therefore, in fact mobile high-pressure washing could be used as a valid variation and alternative of CIP methods using all the advantages that it brings.

To be able to achieve best cleaning results in different applications while resources can be kept significantly low with regard to water and detergent consumption as well as energy consumption, high-pressure cGMP cleaning methods have a huge potential. Furthermore, classical chemical (not using high pressure) CIP methods for very large vessels and holding tanks such as fermenters or storage tanks need significant amounts of water, chemistry, and time to clean. High-pressure applications are coming with the advantage to shorten downtimes of the parts and systems to get cleaned by significantly reducing the time a cleaning process takes, apart from the above-mentioned big advantages of reduction of energy and media consumption.

Figure 2: Examples of parts, bins, and vessels ready to apply high-pressure cleaning as CIP method.

The advantage of mechanical action in high-pressure cleaning

The advantages of high-pressure cleaning can significantly enhance cleaning efficiency. High-pressure cleaning mainly means mechanical cleaning and thus is very effective against resistant contaminants like coatings and organic matter that often build adherend difficult-to-clean residues and crusts. It uses the following physical parameters, while mechanical action becomes the main principle:

1. time
2. temperature
3. mechanical action
4. chemical action
5. coverage/exposure

Since in most cases water is used as the chemical medium to generate the high-pressure stream in pharmaceutical cGMP washing processes, these decisive physical parameters are directly linked to the water supply for the process. The quality of water that is used here is just a minor fact with regards to the cleaning effectiveness itself but of course is closely linked to the quality specifications and final level of cleanliness of the wash goods (bins, IBCs, vessels) the responsible process department sets as specifications. All pharma water qualities (PW, WFI) should be applicable cold and hot. Often higher water temperatures of up to 90 °C are chosen to not only leverage the physical effectiveness of the cleaning procedure itself but also because applying higher temperatures results in a better/faster drying phase of the wash goods afterwards. Detergent could be added in low or adequate concentrations to enhance the cleaning effectiveness against resistant contaminants.

Using innovative well-engineered nozzle design, cleaning with high-pressure systems results in point-of-care cleaning applications with high mechanical effectiveness on the surfaces to get cleaned. The pressure of a water jet created and directed against a surface depends on several factors. There are systems available that create up to 75 bar pressure at a flow rate of just 42 l/min. High-pressure cleaning systems are effective and sustainable at the same time by using high pressure at low flow rates.

The power of the water jet stream impact that is created by a high-pressure washer onto a surface depends on several factors, like on the pattern that is created and on the jet angle. The impact value that is created and working on the surface is usually expressed in kg/cm². To get the impact value calculation of the Total Theoretical Impact (TTI) is necessary. It can be calculated by the following formula, where Q is the flow rate at working pressure in lpm and P is the pressure value in kgp/cm².

$$TTI = 0{,}024 * Q * \sqrt{P} \qquad [\text{kgp/cm}^2]$$

This value must be multiplied with the TTI per Square Centimeter Coefficient E, which results in getting the Spraying Liquid Impact (SLI) also in kgp/cm².

$$SLI = E * TTI \qquad [\text{kgp/cm}^2]$$

The coefficient E depends on the jet nozzle design with regards to general outlet design and spraying angle. Table 1 displays an example of different jet nozzles coefficient E.

For the integration of high-pressure water jet streams in a cleaning process hydrokinetic lances with 2 or more jet nozzles are very convenient. Connected to the high-pressure washer those hydrokinetic lances can be inserted into a vessel at one point or (in bigger vessels) more specific hights with automated hight adjustment. By rotating the hydrokinetic head with the fix attached nozzle jets in 360° an orbital effect and impact can be achieved. Following an orbital 360° pattern the cleaning process can

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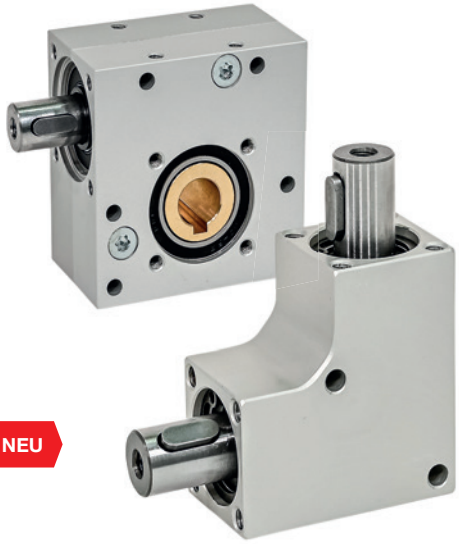

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TTI per Square Centimetre Coefficient E for different jet nozzle designs for 300 mm distance.

TOTAL THEORETICAL IMPACT PER SQ CM COEFFICIENT AT DISTANCE OF 300 MM (E)					
Spray Angle	Flat jet nozzle	Spray Angle	Full cone nozzle	Spray Angle	Hollow cone nozzle
15°	0,300	15°	0,110		
25°	0,180				
35°	0,130	30°	0,025		
40°	0,120				
50°	0,100	50°	0,010		
65°	0,070	65°	0,004		
				60°/80°	0,01/0,02
80°	0,050	80°	0,002		
		100°	0,001		

be guaranteed also in difficult angles in not ideally shaped vessels.

The contamination can be efficiently removed by the targeted application of a high-pressure water jet. Coverage and exposure also play an important role here. Figure 3 shows typical coverage and exposure patterns during high-pressure cleaning. Figure 4 displays a typical hydrokinetic lance with 4 high-pressure nozzles in action during the high-pressure cleaning of an IBC.

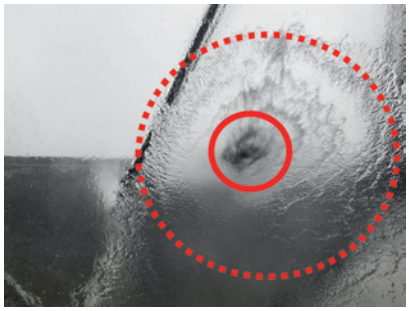

Figure 3: Typical Coverage and exposure pattern with a hydrokinetic jet stream cleaning.

Figure 4: Rotating hydrokinetic lance with 4 nozzles.

The cleaning success depends on the pattern that the hydrokinetic lance traces over the surface of the contaminated vessel. The speed and effectiveness of the cleaning are the decisive parameters to be achieved here. Figure 5 shows such an ideal pattern for high-pressure cleaning with a hydrokinetic lance with 4 nozzles, resulting in a successive and effective cleaning success when removing contamination.

Finally, an optimised cleaning pattern achieves optimum cleaning performance in addition to the high-pressure water jet used. Significant savings can be made in terms of time and media consumption for the water and, if necessary, chemical additives used.

Saving of media consumption in cleaning with high-pressure applications

Sustainability and reduction of media and energy consumption has become a growing concern in pharmaceutical industry. Water and power consumption are critical in general, and cleaning is not an exception here. By using high-pressure cleaning systems both water and power consumption can be reduced with significant ratios. Due to the very effective point of care mechanical effect of high-pressure applications also the time spent on cleaning can be reduced significantly.

Case study – Rapid Mixer Granulator, an onsite test

The effectiveness of manual cleaning of a Rapid Mixer Granulator in pharmaceutical production should be scrutinised. The parameters of time and potential savings in media consumption were decisive criteria. The contamination in the Rapid Mixer Granulator that needs to be removed by cleaning consisted of a compound called Nabumetone, which is completely insoluble in water. The total capacity of the Rapid Mixer Granulator was 600 l. The internal structure of the granulator with its mixing tools is a challenge for both manual and automated cleaning.

The previous time for manual (pressure-less) cleaning of the granulators interior chamber was approximately 3 hours. The high-pressure cleaner used in this cleaning evalua-

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Figure 5: Cleaning exposure pattern of hydrokinetic lance with 4 nozzles.

tion test is called M-Line from IWT Pharma (fig. 6). It is a mobile unit that can work with 75 bar water pressure at 100 % output. As the water pressure available on site was not high enough, the power of the pressure washer was limited to 55 % of its maximum power. The already mentioned complicated internal structure of the mixer was cleaned with a standard high-pressure lance at one position with 4 nozzles. As the contaminant Nabumetone is not water-soluble, a detergent was used in the manual cleaning process before. No detergents have been used in the high-pressure cleaning test evaluation using the M-Line

Figure 6: M-Line mobile high-pressure washer.

though. In fig. 7 there is an exemplary technical scheme of the mobile high-pressure washer connected to a Rapid Mixer Granulator with a hydrokinetic lance attached at a specific position within the vessel.

The cleaning was divided into phases to document the cleaning success. 7 cleaning phases were required to achieve a satisfactory result in terms of optimal cleaning success. Both the parameters and the cleaning success were documented for the individual phases. Table 2 displays the different phases with its parameters and the cleaning success level.

Figure 8 gives an impression of the initial contamination of the Rapid Mixer Granulator. A pre-washing phase was done to remove the coarse impurities. Already after the first cleaning phase (phase 1), which was set to 105 seconds due to the severity of the contamination, a significant cleaning success was achieved. But there were still traces of contamination on the chamber wall and especially on the mixer tools that are more difficult to clean because of its special geometries.

The power output of the high-pressure cleaner pump was reduced from initially 75 % in the pre-phase and 70 % in phase 1 to an average of 55 % output in the following washing phases, which corresponds to a pressure of approx. 35 bar.

At the end of the seventh cleaning phase, a cleaning result was achieved that corresponds with the success of manual cleaning. The final result was optimal cleaning of the chamber and all the tools it contained, such as propeller, chopper, and mill chute (fig. 9).

The results obtained are summarized in table 3. It is clearly visible that significant savings have been achieved in terms of the duration of the cleaning process and in terms of water consumption. Overall, the Rapid Mixer Granulator could be successfully cleaned in 7 min and 45 seconds which is (compared to the previous manual cleaning) a decrease of 95 % in cleaning time spent. Regarding water consumption: while the manual cleaning process required 135 gallons of water, water consumption was reduced to just 45 gallons with the high-pressure washer used above. This is a reduction by 66 %.

The cleaning result was assessed by the operator of the system as an improvement on the previous manual cleaning (table 3). Since the high-pressure washer was only running at 55 % power capacity and no detergent was used, there is more potential for improvement. Running the high-pressure washer at 100 % power capacity and integrating some detergent in the process could

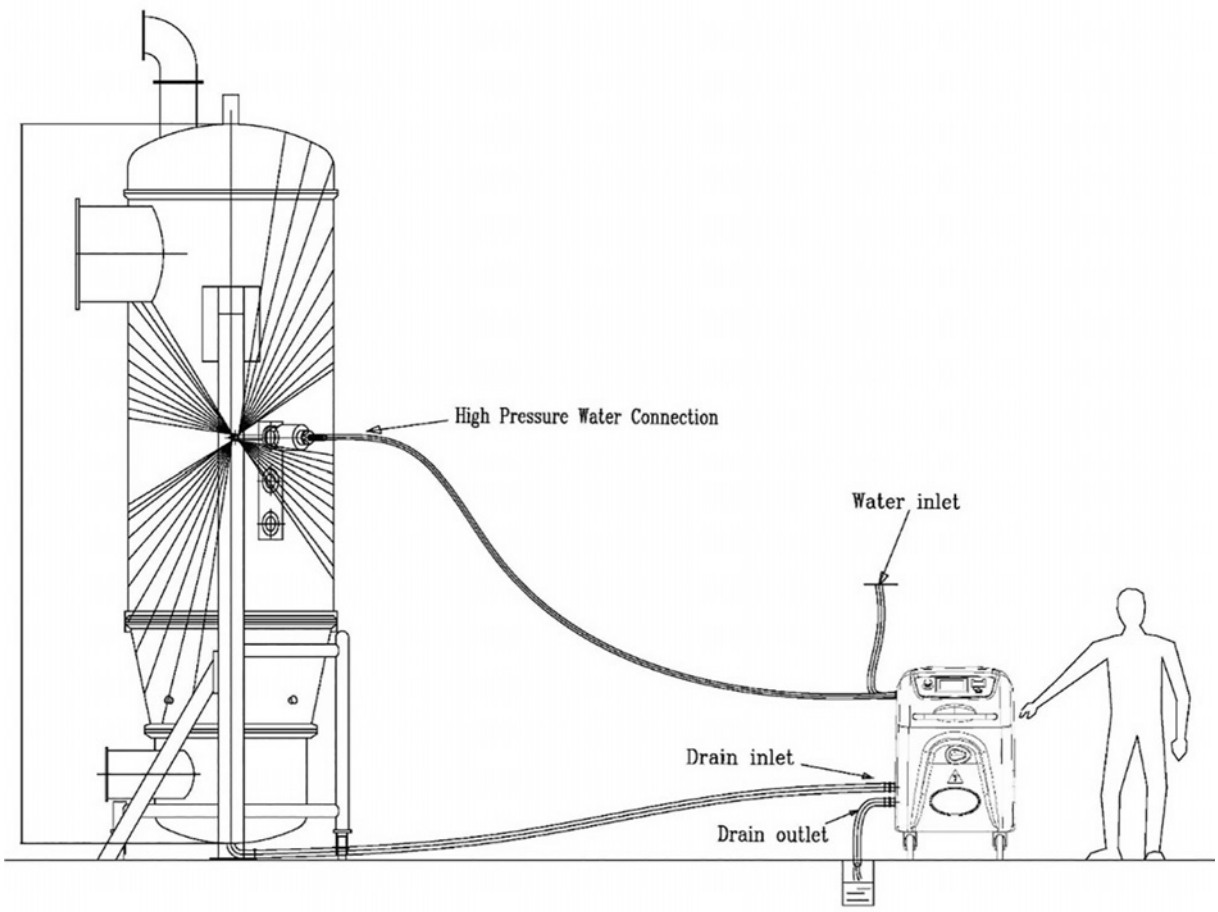

Figure 7: Example of high-pressure CIP application with the mobile high-pressure washer connected to a granulator, with hydrokinetic lance attached in one position.

Documentation of parameters of different washing phases.

Phase	Cycle Time	Detergent	Water Temp	Water Usage	Visual Results
1	60 seconds	No	59° F	26 liters	Dirty
2	105 seconds	No	59° F	46 liters	Dirty
3	60 seconds	No	59° F	22 liters	Dirty
4	60 seconds	No	59° F	20 liters	OK
5	60 seconds	No	59° F	20 liters	Acceptable
6	60 seconds	No	59° F	19 liters	Good
7	60 seconds	No	59° F	20 liters	Excellent
Total	**485 seconds (7:45)**	**None**	**Not Heated**	**173 liters**	**"Equivalent to 3 hours of manual cleaning" - [redacted] operator**

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Table 3

Comparison of the improvement with automated high-pressure washing vs. manual washing.

Metric	Cipla's Manual Cleaning Process	M-Line Cleaning Process	Percent Change
Cleaning Time	Estimated 180 minutes	7 minutes 45 seconds	95% decrease
Water Usage	Estimated 135 gallons	45 gallons	66% decrease
Quality	Acceptable	Excellent	Improved

Figure 8: Initial contamination of the Rapid Mixer Granulator and its interior tools.

further reduce cycle times and media consumption significantly.

The operator of the pharmaceutical production aims to increase their onsite water supply to cleaning equipment area which will increase the efficacy of the high-pressure washer´s performance. Detergent application and dosage through the equipment will be evaluated by Quality Assurance (QA) if necessary.

Summary

High-pressure cleaning applications in the pharmaceutical industry are a valid method for significantly shortening the time frame for cleaning. Downtimes in pharmaceutical production that are used for cleaning equipment can also be transferred into production time spans. In terms of sustainability, the example of a cleaning application presented in this article shows that the use of cGMP-compliant high-pressure applications for cleaning processes can also significantly reduce media and energy consumption.

Finally, the qualification of (validated) systems used in GMP applications is always a must within pharmaceutical industry. Qualification of the cleaning systems must be feasible and applicable through formal and executable qualification documentation. A provider and manufacturer of high-pressure cleaning systems must be aware of these challenges and has to offer such solutions for end users in pharmaceutical GMP production. Also, end users must be supported in finding the best method with high-pressure applications to achieve consistent and reproduceable results in a semi-automated method.

Figure 9: Cleaning success after the final washing cycle, phase 7.

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